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14. ABSTRACT

CHT use has been demonstrated to confer an increased risk of breast cancer. Genetic variation in hormonal pathways may modify the effect of CHT on breast cancer risk. Using 1237 cases and 1015 controls from two population-based case-control studies of breast cancer, we investigated the effect of genetic variation in 7 genes within the progesterone pathway using a tagSNP and functional SNP approach and 5 genes within the catechol estrogen pathway. Within single gene analyses we observed breast cancer risk to be modestly associated with one SNPs in each *GSTP1* (rs1695: OR = 1.4 [95% CI: 1.02-1.9] for carriers of A allele); *CYP1B1* (rs1056827: OR = 1.7]95% CI:1.2-2.5] for T homozygotes); *SRD5A1* (rs248793: OR=1.2 [95% CI: 1.02-1.5] for G homozygotes) and *PGR* (rs492457: OR=1.5 [95% CI: 1.01-2.1] for carriers of the A allele). We found that the breast cancer risk associated with SNPs was particularly strong in long-term CHT users. In a multi-gene model including two genes with single gene effects within the estrogen pathway (*CYP1B1*2* and *GSTP1*), breast cancer risk was 1.6 (95% CI: 1.03-2.4) times higher for carriers of 1 high risk genotype and 2.8 (95% CI: 1.5-5.3) times higher for women with 2 high risk genotypes compared to women with 0 high risk genotypes. The impact of high risk genotypes was stronger in long-term CHT users, particularly in long-term, current CHT users (OR=5.6 [95% CI: 1-5-20.6]). These results suggest that breast cancer risk among CHT users is modified by variation in genes within hormonal pathways.

15. SUBJECT TERMS

Genetic polymorphisms, epidemiology, exogenous risk factors, gene-environment interactions, hormonal pathway, estrogen, progesterone

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Introduction

This document describes the work completed for the duration of the pre-doctoral training grant for the Breast Cancer Research Program for Kerryn Reding (W81XWH-06-1-0312). All of the tasks outlined in the statement of work have been completed.

Body

All tasks outlined for months 1-36 in the statement of work have been completed (Appendix 1.) Firstly, the analysis investigating the effect of pre-diagnostic alcohol consumption on mortality among 1,286 female breast cancer cases has been published in the journal, Cancer Epidemiology Biomarkers and Prevention (Appendix 3). Briefly, we observed that women who consumed alcohol in the 5 years prior to diagnosis had a decreased risk of death [>0 to <3 drinks per week: HR(hazard ratio) = 0.7 (95% CI: 0.6-0.95); 3 to <7 drinks per week: RR = 0.6 (95% CI: 0.4-0.8); ≥ 7 drinks per week: RR = 0.7 (95% CI: 0.5-0.9)] compared to non-drinkers. Additionally, an analysis investigating the effect of pre-diagnostic smoking indicated no increased risk of death among breast cancer cases

Secondly, an analysis investigating the potential for BRCA1 and BRCA2 germline mutations to alter the impact of chemotherapy and Tamoxifen on the risk of asynchronous, contralateral breast cancer (CBC) within 708 women with CBC and 1,399 women with unilateral breast cancer has been completed and a manuscript emanating from this work has been submitted for publication to the Journal of Clinical Oncology. Our findings indicated that the risk of CBC associated with chemotherapy and Tamoxifen did not differ between BRCA1/2 mutation carriers and non-carriers, except perhaps within certain chemotherapy regimens. Chemotherapy was found to reduce the risk of CBC in non-carriers (relative risk [RR] = 0.6 [95% CI: 0.5-0.7]) and carriers (RR = 0.5 [95% CI: 0.2-0.97]).

Finally, data analysis for my dissertation project has been completed. For part 1 of my dissertation, I investigated the effect of genetic variation in the catechol estrogen metabolism pathway on breast cancer risk. We observed a that the risk of breast cancer increased as the number of high risk alleles in the combined *CYP1B1-GSTP1* increased such that women with 1 high risk genotype were at a 1.6-fold increased risk of breast cancer (95% CI: 1.03 – 2.4) , and women carrying 2 high risk genotypes were at a 2.8-fold increased risk (95% CI: 1.5-5.3) compared to women with 0 high risk alleles (test for trend: p-value = 0.03; table 1). Furthermore, we observed the breast cancer risk associated with carrying 1-2 high risk genotypes to be particularly strong for long-term combined hormone therapy (CHT) users (compared to users with 0 high risk genotypes, women with ≥1 high risk genotypes: OR = 3.3 [95% CI 1.02-10.4] among long-term CHT users; OR = 1.9 [95% CI: 0.4-9.3] among short-term CHT users; OR = 1.3 [95% CI 0.8-2.1] among never CHT (Table 2). These data suggest that the risk of breast cancer associated with CHT use is modified by genetic variation in the catechol estrogen pathway. The manuscript detailing our findings has been submitted for publication to the journal, Cancer Epidemiology Biomarkers and Prevention.

For part 2 of my dissertation investigating the effect of variation within 7 genes of the progesterone pathway, data analysis is complete and the manuscript is under preparation. Within this project, we observed breast cancer risk to be modestly associated with one SNP in each of 2 genes: *SRD5A1* (rs248793: OR=1.2 [95% CI: 1.02-1.5] for G homozygotes) and *PGR* (rs492457: OR=1.5 [95% CI: 1.01-2.1] for carriers of

the A allele; table 3). We observed breast cancer risk related to each of these variants to be particularly heightened in long-term CHT users (rs248793: OR = 3.0 [95% CI: 1.6-5.7]; rs492457: OR = 2.0 [95% CI: 0.7-5.7]). However, we did not detect statistically significant gene-CHT interactions within this pathway. This manuscript is currently under co-author review.

As an additional exploration of genetic variation within this hormonal pathway, we chose to explore the potential for rare mutations within the *PGR* gene to be associated with breast cancer. Using long-range PCR techniques to sequence exons 1 and 2 of *PGR*, and a Solexa chip from Illumina which provides deep coverage of this sequence, we have investigated the association between rare polymorphisms and breast cancer within the same population of 2,351 women from my dissertation. This manuscript is currently being prepared.

Key Research Accomplishments

Progression Towards Doctoral Degree

1. Completed Doctoral general exam
2. Completed data analysis investigating genetic variation in the catechol estrogen pathway and breast cancer risk (part 1 of my dissertation)
3. Completed data analysis investigating genetic variation in tagSNPs and functional SNPs within the progesterone pathway and breast cancer risk (part 2 of my dissertation)
4. Prepared manuscripts detailing the findings from my two dissertation projects
5. Defended my Doctoral dissertation

Data Analysis Projects

6. Conducted data analysis and prepared a manuscript leading to publication of findings related to pre-diagnostic alcohol consumption and risk of death among breast cancer patients.
7. Conducted data analysis and prepared a manuscript describing the risk of asynchronous contralateral breast cancer in BRCA1/2 germline mutations in relation to the effect of chemotherapy and Tamoxifen.

Teaching Related Accomplishments

8. Completed data analysis on teaching strategies and presented findings at a Teaching Symposium
9. Taught Introductory to Biostatistics to Masters of Nutrition students at Bastyr University as an adjunct instructor

Reportable Outcomes

Published Manuscript: 'The Effect of Pre-Diagnostic Alcohol Consumption on Survival After Breast Cancer in Young Women,' Kerryn W. Reding, Janet R. Daling, Cecilia A. O'Brien, David R. Doody, Peggy L. Porter, and Kathleen E. Malone. Cancer Epidemiol Biomarkers Prev 2008; 17 1988-1996.

Manuscript, submitted: Kerryn W. Reding, Noel S. Weiss, Chu Chen, Christopher I. Li, Christopher S. Carlson, Jasmine Wilkerson, Federico M. Farin, Kenneth E. Thummel, Janet R. Daling, and Kathleen E. Malone. "Genetic polymorphisms in the catechol estrogen metabolism pathway and breast cancer risk."

Manuscript, submitted: 'Adjuvant systemic therapy for breast cancer and the risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers,' Kerryn W. Reding, Kathleen E. Malone, Bryan Langholz, Colin B. Begg, Leslie Bernstein, Robert W. Haile, Marinela Capinau, Anne Reiner, Xiaolin Liang, Charles F. Lynch, Patrick Concannon, Sharon Teraoka, Lisbeth Bertelsen, Ake Borg, The WECARE Collaborative Study Group, and Jonine Bernstein.

Conclusion

In conclusion, the work completed during the award period has provided insight into potential mechanisms driving breast carcinogenesis, ranging from genes in the hormonal pathways affecting the impact of CHT on breast cancer risk to the effect of *BRCA1/2* mutations on adjuvant therapy in breast cancer to the effect of alcohol consumption on survival in breast cancer.

References

Manuscripts

Kerryn W. Reding, Janet R. Daling, Cecilia A. O'Brien, David R. Doody, Peggy L. Porter, and Kathleen E. Malone. The Effect of Pre-Diagnostic Alcohol Consumption on Survival After Breast Cancer in Young Women. Cancer Epidemiol Biomarkers Prev 2008; 17 1988-1996.

Meeting Abstracts

Era of Hope Conference, Department of Defense Breast Cancer Research Program, Baltimore, MD, June 2008. "Genetic polymorphisms in the catechol estrogen metabolism pathway as modifiers of the effect of hormone therapy in breast cancer risk." Kerryn W. Reding, Chu Chen, Christopher I. Li, Christopher S. Carlson, Jasmine Wilkerson, Frederico M. Farin, Kenneth E. Thummel, Janet R. Daling, and Kathleen E. Malone.

Center for Ecogenetics and Environmental Health Annual Retreat, University of Washington, Seattle, WA, November 2007. "Genetic polymorphisms in the catechol estrogen metabolism pathway as modifiers of the effect of hormone therapy in breast cancer risk." Kerryn W. Reding, Chu Chen, Christopher I. Li, Christopher S. Carlson, Jasmine Wilkerson, Frederico M. Farin, Kenneth E. Thummel, Janet R. Daling, and Kathleen E. Malone.

4th Annual University of Washington Teaching and Learning Symposium, Seattle, WA, May 2008. "Innovative Teaching Methods for a Large Introductory Epidemiology Course." Yuzo Arima, Kerryn W. Reding, Britton Trabert, Zoe Edelstein, Sara Nelson, Kathryn Adeney, Amy Poel, and Jack Goldberg.

American Association of Cancer Researchers (AACR) Annual Meeting, Los Angeles, CA, April 2007, "Genetic polymorphisms in the estrogen metabolism pathway as modifiers of the effect of hormone therapy in breast cancer risk." Kerryn W. Reding, Chu Chen, Christopher I. Li, Christopher S. Carlson, Jasmine Wilkerson, Frederico M. Farin, Kenneth E. Thummel, Janet R. Daling, and Kathleen E. Malone.

2nd Annual University of Washington Teaching and Learning Symposium, Seattle, WA, April 2006. "Using Formative Assessments as a Student-Centered Approach to Improving the Implementation of Problem-Based Learning Modules." Kerryn W. Reding, Deborah Hatch, Lawrence Wechsler, and Thomas D. Koepsell.

Table 1. The risk of breast cancer associated with genetic variation modeled as *CYP1B1**2- *GSTP1*gene-gene interactions

Case n (%)[1]	**Control n (%)**[1]	**# High Risk Genotypes**[2]		**OR**[3]	**95% CI**	
79 (9.0)	108 (12.6)	0 high risk		1.0 (ref)		
724 (82.6)	704 (82.4)	1 high risk		1.6	1.0**	2.4
74 (8.4)	42 (4.9)	2 high risk		2.8	1.5	5.3
					$p_{trend} = 0.03$	
		GSTP1	***CYP1B1*2***			
79 (9.0)	108 (12.6)	0	0	1.0 (ref)		
10 (1.1)	8 (0.9)	0	1	1.8	0.6	5.1
714 (81.4)	696 (81.5)	1	0	1.5	1.0	2.4
74 (8.4)	42 (4.9)	1	1	2.8	1.5	5.3
					$p_{int} = 0.36$	

** due to rounding, p-value < 0.05

1. Some percentages do not sum to 100% due to rounding
2. High risk genotypes as determined in the single gene analyses: A/A and A/G for *GSTP1* and T/T for *CYP1B1*.
3. Adjusted for age and year of diagnosis (reference date for controls)

Table 2. The risk of breast cancer associated with genetic variation as investigated in the *CYP1B1*2-GSTP1* multi-gene model stratified by CHT use

HT Use	Case	Control	# High Risk Genotypes	OR[1]	95% CI	
CHT						
Never CHT Users						
	61 (9.5)	85 (12.6)	0	1.0 (ref)		
	579 (90.5)	591 (87.4)	1-2	1.3	0.8	2.1
CHT: < 60 months of use						
	4 (5.0)	9 (11.4)	0	1.0 (ref)		
	76 (95.0)	70 (88.6)	1-2	1.9	0.4	9.3
CHT: ≥ 60 months of use						
	14 (9.1)	14 (14.9)	0	1.0 (ref)		
	140 (90.9)	80 (85.1)	1-2	3.3	1.0**	10.4
					p_{int} =0.42	
EHT[2]						
Never EHT Users						
	25 (9.2)	42 (13.7)	0	1.0 (ref)		
	247 (90.8)	265 (86.3)	1-2	0.8	0.4	1.7
EHT: < 60 months of use						
	11 (9.9)	9 (6.8)	0	1.0 (ref)		
	100 (90.1)	124 (93.2)	1-2	1.0	0.3	3.5
EHT:≥ 60 months of use						
	23 (9.1)	34 (14.4)	0	1.0 (ref)		
	229 (90.9)	202 (85.6)	1-2	2.2	1.0**	4.9
					p_{int} = 0.17	

** due to rounding, p-value < 0.05

1. Adjusted for age and year of diagnosis (reference date for controls)
2. Exclusive EHT users only

Table 3. The risk of breast cancer overall and specific histologic types associated with single SNPs in *PGR, AKR1C1, AKR1C2, AKR1C3, SRD5A1, SRD5A2* and *CYP3A4*

			Breast caner overall					Ductal				Lobular				
Gene	**SNP**	**Geno-type**	**Control n (%)[1]**	**Case n (%)[1]**	**OR[2]**	**95% CI**		**Case n (%)[1]**	**OR[2]**	**95% CI**		**Case n (%)[1]**	**OR[2]**	**95%**		**p-value[3]**
PGR																
	rs500760	A/A	592 (58.6)	715 (57.9)	1.0 (ref)			434 (57.0)	1.0 (ref)			154 (55.4)	1.0 (ref)			
		A/G	348 (34.5)	456 (37.0)	0.9	0.8	1.1	286 (37.5)	0.9	0.8	1.1	107 (38.5)	1.0	0.7	1.3	0.62
		G/G	70 (6.9)	63 (5.1)	0.9	0.6	1.3	42 (5.5)	0.9	0.6	1.4	17 (3.8)	1.1	0.6	1.9	0.82
	rs1042839	CC	727 (70.7)	896 (70.4)	1.0 (ref)			540 (70.0)	1.0 (ref)			200 (70.4)	1.0 (ref)			
	(PROGINS)	CT	274 (26.6)	343 (27.0)	1.0	0.8	1.2	213 (27.6)	1.0	0.8	1.3	77 (27.1)	1.0	0.7	1.4	0.66
		TT	28 (2.7)	33 (2.6)	0.8	0.5	1.5	18 (2.3)	0.8	0.5	1.5	7 (2.5)	0.9	0.4	2.1	0.67
	rs1042838	GG	664 (68.4)	803 (67.3)	1.0 (ref)			485 (67.2)	1.0 (ref)			180 (67.4)	1.0 (ref)			
	(PROGINS)	GT	280 (28.8)	357 (29.9)	1.1	0.9	1.3	219 (30.3)	1.0	0.8	1.3	80 (30.0)	1.1	0.8	1.4	0.76
		TT	27 (2.8)	33 (2.8)	0.9	0.5	1.5	18 (2.5)	0.9	0.5	1.6	7 (2.6)	0.9	0.4	2.2	0.68
	rs3740753	C/C	717 (73.5)	882 (73.1)	1.0 (ref)			539 (72.9)	1.0 (ref)			194 (73.5)	1.0 (ref)			
		C/G	230 (23.6)	294 (24.4)	1.0	0.8	1.3	183 (24.8)	1.1	0.8	1.3	63 (28.9)	1.0	0.7	1.4	0.84
		G/G	28 (2.9)	31 (2.6)	0.8	0.5	1.4	17 (2.3)	0.8	0.4	1.4	7 (2.6)	0.9	0.4	2.2	0.62
	rs11224552	C/C	736 (72.1)	928 (73.1)	1.0 (ref)			560 (72.6)	1.0 (ref)			209 (73.3)	1.0 (ref)			
		C/T	260 (25.5)	311 (24.5)	1.0	0.8	1.2	191 (24.8)	1.0	0.8	1.2	71 (24.9)	1.0	0.8	1.4	0.99
		T/T	25 (2.4)	30 (2.4)	1.2	0.7	2.1	20 (2.6)	1.3	0.7	2.4	5 (1.8)	0.8	0.3	2.3	0.80
	rs484389	T/T	509 (55.4)	641 (55.9)	1.0 (ref)			389 (56.1)	1.0 (ref)			142 (55.2)	1.0 (ref)			
		T/C	349 (38.0)	434 (37.8)	1.0	0.8	1.2	262 (37.8)	1.0	0.8	1.2	97 (37.7)	1.0	0.7	1.3	0.92
		C/C	60 (6.5)	72 (6.3)	0.9	0.6	1.3	42 (6.1)	0.9	0.6	1.3	18 (7.0)	1.1	0.6	1.9	0.80
	rs558959	T/T	566 (55.7)	708 (56.7)	1.0 (ref)			429 (56.6)	1.0 (ref)			156 (56.3)	1.0 (ref)			
		T/C	391 (38.5)	469 (37.6)	1.0	0.8	1.1	287 (37.9)	1.0	0.8	1.2	103 (37.2)	1.0	0.7	1.3	0.72
		C/C	59 (5.8)	72 (5.8)	0.9	0.7	1.4	42 (5.5)	0.9	0.6	1.4	18 (6.5)	1.1	0.6	2.0	0.83
	rs492457	A/A	715 (57.9)	592 (58.6)	1.0 (ref)			433 (58.0)	1.0 (ref)			162 (58.5)	1.0 (ref)			
		A/G	456 (37.0)	348 (34.5)	1.0	0.9	1.3	272 (36.5)	1.1	0.9	1.3	100 (36.1)	1.0	0.8	1.4	0.11

	G/G	63 (5.1)	70 (6.9)	0.7*	0.5	1.0	41 (5.5)	0.8	0.5	1.2	15 (5.4)	0.7	0.4	1.3	0.13
rs543936	A/A	610 (58.8)	732 (57.5)	1.0 (ref)			444 (57.4)	1.0 (ref)			168 (58.3)	1.0 (ref)			
	A/G	358 (34.5)	477 (37.4)	1.1	0.9	1.3	288 (37.2)	1.1	0.9	1.3	104 (36.1)	1.0	0.8	1.4	0.72
	G/G	69 (6.6)	65 (5.1)	0.8	0.5	1.1	42 (5.4)	0.8	0.6	1.2	16 (5.6)	0.7	0.4	1.3	0.22
rs635984	C/C	260 (27.9)	307 (27.2)	1.0 (ref)			185 (26.8)	1.0 (ref)			68 (26.8)	1.0 (ref)			
	C/G	409 (43.9)	521 (46.2)	1.0	0.8	1.3	324 (47.0)	1.1	0.9	1.4	118 (46.5)	1.1	0.7	1.5	0.73
	G/G	262 (28.1)	299 (26.5)	0.9	0.7	1.1	181 (26.2)	0.9	0.7	1.2	68 (26.8)	0.9	0.6	1.4	0.57
rs503602	C/C	739 (74.6)	912 (74.7)	1.0 (ref)			566 (76.1)	1.0 (ref)			193 (71.2)	1.0 (ref)			
	C/A	231 (23.3)	287 (23.5)	1.0	0.8	1.2	164 (22.0)	0.9	0.7	1.2	73 (26.9)	1.2	0.9	1.7	0.14
	A/A	20 (2.0)	22 (1.8)	1.0	0.5	1.8	14 (1.9)	1.0	0.5	2.0	5 (1.8)	1.1	0.4	3.0	0.94
rs516693	G/G	777 (75.3)	961 (75.6)	1.0 (ref)			587 (76.2)	1.0 (ref)			209 (72.8)	1.0 (ref)			
	G/A	239 (23.2)	295 (23.2)	1.0	0.8	1.2	173 (22.5)	1.0	0.8	1.2	74 (25.8)	1.2	0.9	1.6	0.37
	A/A	16 (1.6)	15 (1.2)	0.8	0.4	1.6	10 (1.3)	0.8	0.4	1.9	4 (1.4)	1.0	0.3	3.2	0.81
rs529359	A/A	438 (42.2)	515 (40.4)	1.0 (ref)			310 (40.0)	1.0 (ref)			119 (41.5)	1.0 (ref)			
	A/G	451 (43.5)	599 (47.0)	1.1	1.0	1.4	356 (46.0)	1.1	0.9	1.4	135 (47.0)	1.1	0.9	1.5	0.42
	G/G	148 (14.3)	161 (12.6)	1.0	0.7	1.3	108 (14.0)	1.1	0.8	1.5	33 (11.5)	0.8	0.5	1.3	0.27
rs542384	A/A	702 (67.8)	847 (66.4)	1.0 (ref)			505 (65.2)	1.0 (ref)			191 (66.6)	1.0 (ref)			
	A/T	289 (27.9)	374 (29.3)	1.1	0.9	1.4	227 (29.3)	1.1	0.9	1.4	88 (30.7)	1.2	0.9	1.7	0.45
	T/T	45 (4.3)	54 (4.2)	1.3	0.8	1.9	43 (5.6)	1.6	1.0	2.6	8 (2.8)	0.8	0.4	1.8	0.03
rs11224589	A/A	478 (48.1)	600 (48.5)	1.0 (ref)			374 (50.0)	1.0 (ref)			131 (47.3)	1.0 (ref)			
	A/C	431 (43.4)	551 (44.5)	1.0	0.8	1.2	330 (44.1)	1.0	0.8	1.2	123 (44.4)	1.0	0.7	1.3	0.87
	C/C	85 (8.6)	86 (7.0)	0.7	0.5	1.0	44 (5.9)	0.6*	0.4	1.0	23 (8.3)	0.8	0.5	1.4	0.06
rs506487	C/C	432 (4.7)	557 (43.8)	1.0 (ref)			336 (43.8)	1.0 (ref)			131 (45.5)	1.0 (ref)			
	C/T	446 (43.1)	570 (44.8)	1.1	0.9	1.3	348 (45.3)	1.1	0.9	1.3	122 (42.4)	0.9	0.7	1.2	0.81
	T/T	126 (12.2)	144 (11.3)	0.9	0.7	1.2	84 (10.9)	0.9	0.7	1.2	35 (12.2)	0.9	0.6	1.5	0.78
rs10895068	GG	910 (89.1)	1128 (89.2)	1.0 (ref)			687 (89.7)	1.0 (ref)			248 (87.9)	1.0 (ref)			
(+331)	GA	107 (10.5)	131 (10.4)	1.1	0.8	1.4	77 (10.0)	1.0	0.7	1.3	31 (11.0)	1.1	0.7	1.6	0.63
	AA	4 (0.4)	5 (0.4)	1.0	0.3	3.8	2 (0.3)	0.6	0.1	3.6	3 (1.1)	3.0	0.7	14.0	0.38

rs948516	A/A	491 (49.8)	594 (48.4)	1.0 (ref)			369 (49.7)	1.0 (ref)			135 (48.0)	1.0 (ref)			
	A/G	385 (39.0)	502 (40.9)	1.1	0.9	1.3	289 (39.0)	1.0	0.8	1.2	123 (43.8)	1.2	0.9	1.6	0.22
	G/G	111 (11.2)	132 (10.8)	1.0	0.7	1.3	84 (11.3)	1.0	0.7	1.4	23 (8.2)	0.7	0.4	1.2	0.75
rs521488	C/C	296 (30.7)	362 (30.8)	1.0 (ref)			229 (32.0)	1.0 (ref)			78 (29.8)	1.0 (ref)			
	C/T	479 (49.7)	575 (48.9)	0.9	0.8	1.1	336 (46.9)	0.9	0.7	1.1	142 (54.2)	1.1	0.8	1.5	0.37
	T/T	188 (19.5)	238 (20.3)	1.0	0.8	1.3	151 (21.1)	1.0	0.8	1.3	42 (16.0)	0.8	0.5	1.3	0.96
AKR1C1/2															
rs2854482	T/T	966 (93.2)	1176 (92.1)	1.0 (ref)			709 (91.5)	1.0 (ref)			270 (94.1)	1.0 (ref)			
	T/A	69 (6.7)	98 (7.7)	1.2	0.8	1.6	64 (8.3)	1.3	0.9	1.8	17 (5.9)	1.0	0.6	1.7	0.44
	A/A	1 (0.1)	3 (0.2)	2.2	0.2	22.0	2 (0.3)	2.7	0.2	30.5	0 (0.0)	-			0.74
rs3890593	C/C	519 (54.4)	662 (57.4)	1.0 (ref)			422 (59.4)	1.0 (ref)			136 (54.4)	1.0 (ref)			
	C/T	359 (37.6)	396 (34.4)	0.9	0.7	1.1	236 (33.2)	0.8	0.7	1.0	91 (36.4)	1.0	0.7	1.3	0.11
	T/T	76 (8.0)	95 (8.2)	1.0	0.7	1.4	52 (7.3)	0.9	0.6	1.2	23 (9.2)	1.2	0.7	2.0	0.56
rs11252864	C/C	372 (36.8)	437 (34.8)	1.0 (ref)			259 (34.0)	1.0 (ref)			96 (34.2)	1.0 (ref)			
	C/G	454 (44.9)	591 (47.0)	1.1	0.9	1.3	354 (46.5)	1.1	0.9	1.4	144 (51.2)	1.2	0.9	1.6	0.51
	G/G	186 (18.4)	229 (18.2)	1.1	0.8	1.4	149 (20.0)	1.2	0.9	1.6	41 (14.6)	0.9	0.6	1.3	0.45
rs7915365	C/C	312 (30.0)	374 (29.3)	1.0 (ref)			240 (30.9)	1.0 (ref)			72 (25.1)	1.0 (ref)			
	C/G	511 (49.2)	609 (47.6)	1.0	0.8	1.2	372 (47.9)	0.9	0.7	1.2	142 (49.5)	1.2	0.9	1.6	0.43
	G/G	216 (20.8)	295 (23.1)	1.1	0.9	1.4	164 (21.1)	1.0	0.8	1.3	73 (25.4)	1.5	1.0	2.1	0.03
rs1937865	A/A	473 (48.6)	604 (50.2)	1.0 (ref)			378 (51.8)	1.0 (ref)			129 (48.0)	1.0 (ref)			
	A/C	423 (43.4)	494 (41.1)	0.9	0.7	1.1	281 (38.5)	0.8	0.7	1.0	116 (43.1)	1.0	0.7	1.3	0.10
	C/C	78 (8.0)	105 (8.7)	1.0	0.7	1.4	71 (9.7)	1.1	0.8	1.5	24 (8.9)	1.0	0.6	1.7	0.44
AKR1C3															
rs12529	C/C	367 (39.0)	499 (43.4)	1.0 (ref)			305 (43.7)	1.0 (ref)			116 (43.8)	1.0 (ref)			
	C/G	429 (15.3)	489 (42.5)	0.8	0.7	1.0	284 (40.7)	0.8	0.7	1.0	112 (42.3)	0.8	0.6	1.1	0.13
	G/G	144 (15.3)	163 (14.2)	0.9	1.4	1.2	109 (15.6)	1.0	0.7	1.3	37 (14.0)	0.9	0.6	1.4	0.73
rs12387	A/A	698 (68.0)	838 (66.4)	1.0 (ref)			511 (66.8)	1.0 (ref)			181 (63.7)	1.0 (ref)			
	A/G	303 (29.5)	386 (30.6)	1.1	0.9	1.3	230 (30.1)	1.0	0.8	1.3	93 (32.8)	1.2	0.9	1.6	0.72
	G/G	26 (2.5)	39 (3.1)	1.3	0.8	2.2	24 (3.1)	1.3	0.7	2.3	10 (3.5)	1.5	0.7	3.2	0.63

	rs7086771	G/G	431 (42.3)	525 (41.7)	1.0 (ref)			315 (41.3)	1.0 (ref)			118 (42.0)	1.0 (ref)			
		G/C	462 (45.4)	572 (45.4)	1.1	0.9	1.3	344 (45.1)	1.0	0.8	1.3	132 (47.0)	1.1	0.8	1.4	0.84
		C/C	125 (12.3)	163 (12.9)	1.2	0.9	1.5	104 (13.6)	1.2	0.9	1.6	31 (11.0)	0.9	0.6	1.5	0.50
	rs3209896	A/A	350 (34.6)	412 (33.0)	1.0 (ref)			250 (32.9)	1.0 (ref)			89 (31.9)	1.0 (ref)			
		A/G	493 (48.8)	604 (48.4)	1.1	0.9	1.3	356 (46.9)	1.0	0.8	1.3	144 (51.6)	1.2	0.9	1.6	0.42
		G/G	168 (16.6)	232 (18.6)	1.3	1.0	1.6	153 (20.2)	1.3	1.0	1.8	46 (16.5)	1.1	0.7	1.7	0.12
	rs2298305	G/G	791 (79.0)	951 (76.9)	1.0 (ref)			584 (77.2)	1.0 (ref)			205 (75.4)	1.0 (ref)			
		G/T	201 (20.1)	275 (22.5)	1.1	0.9	1.4	166 (22.0)	1.1	0.9	1.4	64 (23.5)	1.2	0.9	1.7	0.51
		T/T	9 (0.9)	10 (0.8)	1.1	0.4	2.7	6 (0.8)	1.0	0.3	2.7	3 (1.1)	1.6	0.4	6.0	0.82
	rs3750566	T/T	709 (69.7)	869 (69.6)	1.0 (ref)			520 (68.5)	1.0 (ref)			206 (73.8)	1.0 (ref)			
		T/C	272 (26.8)	339 (27.2)	1.0	0.9	1.3	208 (27.4)	1.1	0.9	1.3	68 (24.4)	0.9	0.6	1.2	0.84
		C/C	36 (3.5)	40 (3.2)	1.0	0.6	1.7	31 (4.1)	1.3	0.8	2.2	5 (1.8)	0.5	0.2	1.4	0.29
	rs11252936	A/A	430 (42.7)	524 (42.2)	1.0 (ref)			326 (43.1)	1.0 (ref)			123 (44.4)	1.0 (ref)			
		A/T	451 (44.8)	552 (44.4)	0.9	0.8	1.1	326 (43.1)	0.9	0.7	1.1	118 (42.6)	0.9	0.6	1.2	0.67
		T/T	125 (12.4)	167 (13.4)	1.1	0.8	1.4	104 (13.8)	1.1	0.8	1.4	36 (13.0)	1.0	0.6	1.5	0.89
	rs11252937	T/T	434 (42.6)	530 (41.9)	1.0 (ref)			331 (43.2)	1.0 (ref)			123 (43.6)	1.0 (ref)			
		T/C	460 (45.1)	567 (44.9)	0.9	0.8	1.1	332 (43.3)	0.9	0.7	1.1	123 (43.6)	0.9	0.7	1.2	0.63
		C/C	125 (12.3)	167 (13.2)	1.0	0.8	1.4	103 (13.4)	1.0	0.8	1.4	36 (12.8)	1.0	0.6	1.5	0.94
SRD5A1																
	rs248793	G/G	363 (30.0)	263 (26.5)	1.0 (ref)			222 (30.4)	1.0 (ref)			80 (29.1)	1.0 (ref)			
		C/G	567 (46.9)	507 (51.2)	0.8*	0.6	1.0	333 (45.7)	0.8	0.4	1.0	134 (48.7)	0.8	0.6	1.1	0.38
		C/C	279 (23.1)	221 (22.3)	0.9	0.7	1.1	174 (23.9)	0.9	0.7	1.2	61 (22.2)	0.9	0.6	1.3	0.80
	rs3822430	T/T	417 (40.1)	516 (40.3)	1.0 (ref)			297 (38.3)	1.0 (ref)			118 (41.1)	1.0 (ref)			
		T/C	479 (46.1)	566 (44.2)	1.0	0.8	1.2	363 (46.8)	1.1	0.9	1.3	124 (43.2)	0.9	0.7	1.2	0.31
		C/C	144 (13.8)	198 (15.5)	1.1	0.9	1.4	116 (15.0)	1.1	0.8	1.5	45 (15.7)	1.1	0.7	1.6	0.72
	rs3736316	C/C	415 (40.1)	514 (40.2)	1.0 (ref)			297 (38.4)	1.0 (ref)			118 (41.0)	1.0 (ref)			
		C/T	479 (46.3)	565 (44.2)	1.0	0.8	1.2	360 (46.5)	1.1	0.9	1.3	125 (43.4)	0.9	0.7	1.2	0.39
		T/T	141 (13.6)	198 (15.5)	1.1	0.9	1.5	117 (15.1)	1.2	0.9	1.5	45 (15.6)	1.1	0.8	1.7	0.61
	rs7720479	A/A	402 (40.2)	484 (39.6)	1.0 (ref)			279 (37.7)	1.0 (ref)			109 (39.8)	1.0 (ref)			

		A/G	455 (45.5)	541 (44.2)	1.0	0.8	1.2	345 (46.6)	1.1	0.9	1.3	120 (43.8)	1.0	0.7	1.3	0.42
		G/G	143 (14.3)	198 (16.2)	1.1	0.9	1.5	116 (15.7)	1.2	0.9	1.6	45 (16.4)	1.2	0.8	1.7	0.56
	rs4702379	C/C	617 (59.7)	793 (62.7)	1.0 (ref)			490 (63.7)	1.0 (ref)			180 (63.2)	1.0 (ref)			
		C/T	362 (35.0)	408 (32.2)	0.9	0.7	1.1	239 (31.1)	0.8	0.7	1.0	93 (32.6)	1.0	0.7	1.2	0.21
		T/T	54 (5.2)	64 (5.1)	0.9	0.6	1.3	40 (5.2)	0.9	0.6	1.4	12 (4.2)	0.7	0.4	1.4	0.69
	rs8192165	T/T	298 (30.3)	413 (33.3)	1.0 (ref)			258 (34.1)	1.0 (ref)			89 (32.4)	1.0 (ref)			
		T/DEL	461 (47.0)	531 (42.8)	0.8	0.7	1.0	314 (41.5)	0.8	0.6	1.0	121 (44.0)	0.8	0.6	1.1	0.08
		DEL/ DEL	223 (22.7)	297 (23.9)	0.9	0.7	1.2	185 (24.4)	0.9	0.7	1.2	65 (23.6)	0.9	0.6	1.3	0.88
	rs1651074	C/C	733 (73.9)	879 (71.7)	1.0 (ref)			541 (72.9)	1.0 (ref)			196 (71.0)	1.0 (ref)			
		C/T	231 (23.3)	324 (26.4)	1.2	1.0	1.4	193 (26.0)	1.1	0.9	1.4	71 (25.7)	1.2	0.9	1.6	0.36
		T/T	28 (2.8)	23 (1.9)	0.7	0.4	1.3	8 (1.1)	0.4	0.2	0.9	9 (3.3)	1.4	0.7	3.2	0.03
	rs531241	G/G	400 (32.8)	289 (28.7)	1.0 (ref)			248 (33.3)	1.0 (ref)			87 (31.4)	1.0 (ref)			
		A/G	562 (46.0)	506 (50.3)	0.8*	0.6	1.0	333 (44.7)	0.8	0.4	0.9	133 (48.0)	0.8	0.6	1.1	0.05
		A/A	259 (21.2)	211 (21.0)	0.9	0.7	1.1	164 (22.0)	0.9	0.7	1.2	57 (20.6)	0.8	0.6	1.2	0.58
	rs824811	T/T	658 (65.1)	779 (63.0)	1.0 (ref)			476 (63.8)	1.0 (ref)			163 (57.8)	1.0 (ref)			
		T/C	302 (29.9)	395 (31.9)	1.1	0.9	1.3	225 (30.2)	1.0	0.8	1.3	109 (38.6)	1.4*	1.0	1.8	0.17
		C/C	51 (5.0)	63 (5.1)	1.0	0.7	1.5	45 (6.0)	1.2	0.8	1.8	10 (3.6)	0.7	0.4	1.5	0.34
	rs13974	A/A	668 (67.5)	806 (66.2)	1.0 (ref)			486 (65.2)	1.0 (ref)			179 (66.3)	1.0 (ref)			
		A/G	281 (28.4)	348 (28.6)	1.0	0.8	1.2	216 (29.0)	1.0	0.8	1.3	74 (27.4)	0.9	0.7	1.3	0.77
		G/G	41 (4.1)	64 (5.2)	1.3	0.9	2.0	43 (5.8)	1.4	0.9	2.2	17 (6.3)	1.6	0.9	2.9	0.26
	rs30434	G/G	391 (39.3)	493 (40.3)	1.0 (ref)			310 (41.8)	1.0 (ref)			100 (36.5)	1.0 (ref)			
		G/A	466 (46.8)	540 (44.2)	0.9	0.7	1.1	313 (42.2)	0.8	0.7	1.0	130 (47.4)	1.1	0.8	1.4	0.18
		A/A	138 (13.9)	189 (15.5)	1.1	0.9	1.5	118 (15.9)	1.1	0.8	1.5	44 (16.1)	1.3	0.9	2.0	0.75
SRD5A2																
	rs523349	CC	520 (50.3)	640 (50.3)	1.0 (ref)			394 (51.0)	1.0 (ref)			138 (48.2)				
		CG	421 (40.7)	517 (40.6)	1.0	0.9	1.2	310 (40.1)	1.0	0.8	1.2	120 (42.0)	1.1	0.8	1.4	0.65
		GG	93 (9.0)	116 (9.1)	1.0	0.7	1.4	69 (8.9)	1.0	0.7	1.4	28 (9.8)	1.1	0.7	1.8	0.97
	rs765138	C/C	372 (37.5)	458 (37.2)	1.0 (ref)			281 (37.5)	1.0 (ref)			95 (34.6)	1.0 (ref)			

		C/A	474 (47.8)	574 (46.6)	1.0	0.8	1.2	347 (46.3)	1.0	0.8	1.2	132 (48.0)	1.1	0.7	1.4	0.70
		A/A	146 (14.7)	200 (16.2)	1.1	0.8	1.4	121 (16.2)	1.1	0.8	1.5	48 (17.4)	1.2	0.8	1.8	0.57
	rs632148	G/G	507 (49.3)	627 (49.4)	1.0 (ref)			385 (49.9)	1.0 (ref)			138 (48.6)	1.0 (ref)			
		G/C	416 (40.5)	515 (40.6)	1.0	0.9	1.2	311 (40.3)	1.0	0.8	1.2	116 (40.8)	1.0	0.8	1.4	0.85
		C/C	105 (10.2)	127 (10.0)	1.0	0.7	1.3	76 (9.8)	1.0	0.7	1.3	30 (10.6)	1.0	0.7	1.6	0.95
	rs559555	T/T	341 (32.9)	413 (32.3)	1.0 (ref)			251 (32.3)	1.0 (ref)			89 (30.9)	1.0 (ref)			
		T/A	486 (46.9)	617 (48.2)	1.1	0.9	1.3	376 (48.4)	1.1	0.9	1.3	135 (46.9)	1.1	0.8	1.5	0.82
		A/A	210 (20.2)	249 (19.5)	1.0	0.8	1.2	150 (19.3)	1.0	0.7	1.3	64 (22.2)	1.1	0.8	1.7	0.87
	rs693918	C/C	360 (34.9)	455 (35.8)	1.0 (ref)			274 (35.5)	1.0 (ref)			100 (35.0)	1.0 (ref)			
		C/T	471 (45.7)	590 (46.4)	1.0	0.9	1.2	357 (46.3)	1.0	0.8	1.2	139 (48.6)	1.1	0.8	1.5	0.82
		T/T	200 (19.4)	226 (17.8)	0.9	0.7	1.1	140 (18.2)	0.9	0.7	1.2	47 (16.4)	0.8	0.5	1.2	0.42
	rs589427	A/A	505 (49.9)	623 (49.9)	1.0 (ref)			375 (49.4)	1.0 (ref)			138 (49.6)	1.0 (ref)			
		A/T	415 (41.0)	505 (40.5)	1.0	0.8	1.2	312 (41.1)	1.0	0.8	1.2	113 (40.6)	1.0	0.7	1.3	0.96
		T/T	92 (9.1)	120 (9.6)	1.1	0.8	1.4	72 (9.5)	1.1	0.8	1.5	27 (9.7)	1.0	0.6	1.7	0.93
CYP3A4																
	rs12333983	T/T	791 (77.8)	985 (78.4)	1.0 (ref)			603 (79.2)	1.0 (ref)			217 (77.2)	1.0 (ref)			
		T/A	199 (19.6)	251 (20.0)	1.0	0.8	1.3	143 (18.8)	1.0	0.8	1.2	61 (21.7)	1.3	0.9	1.8	0.15
		A/A	27 (2.6)	21 (1.7)	0.8	0.4	1.4	15 (2.0)	0.8	0.4	1.6	3 (1.1)	0.5	0.2	1.8	0.56
	rs2246709	A/A	546 (53.5)	650 (51.6)	1.0 (ref)			403 (52.7)	1.0 (ref)			144 (51.2)	1.0 (ref)			
		A/G	389 (38.1)	505 (40.1)	1.1	0.9	1.3	301 (39.4)	1.1	0.9	1.3	113 (40.2)	1.2	0.9	1.5	0.38
		G/G	86 (8.4)	104 (8.3)	1.1	0.8	1.4	61 (8.0)	1.0	0.7	1.4	24 (8.5)	1.2	0.7	2.0	0.61
	rs2740574	AA	921 (91.0)	1150 (92.2)	1.0 (ref)			700 (92.5)	1.0 (ref)			258 (92.8)	1.0 (ref)			
	(*1B)	AG	79 (7.8)	90 (7.2)	1.0	0.7	1.3	53 (7.0)	0.9	0.6	1.3	19 (6.8)	1.0	0.6	1.7	0.85
		GG	11 (1.1)	7 (0.6)	0.6	0.2	1.6	4 (0.5)	0.5	0.1	1.7	1 (0.4)	0.4	0.1	3.2	0.34

* statistically significant at the prior probability level of 0.1 in FPRP

1. Some percentages may not sum to 100 due to rounding

2. Adjusted for age at diagnosis (reference date for controls), race, and study

3. testing heterogeneity between breast cancer histologic types

Appendix 1: Statement of Work.

TASK	STATUS
Task 1: Preparation for Lab Work (Months 1-4)	
a. Obtain Institutional Review Board approval	Completed
b. Identify and prepare blood samples for DNA extraction (sample size (n) =2362)	Completed
i. place samples in random order, intermixing cases and controls along with 10% quality control samples	Completed
c. Coordinate the delivery/shipping of extracted DNA to CEEH and TGen	Completed
d. Identify tagSNPs for AKR1C1 based on resequencing data (n = 24)	Completed
e. Choose tagSNPs for AKR1C2, AKR1C3, SRD5A1, SRD5A2, PGR (SNPs already chosen for CYP1B1, COMT, and GSTs)	Completed
Task 2: Coursework and Training-related Work (Months 1-12)	
a. Complete courses:	
i. Gene Structure and Function	Completed; modified task[1]
ii. Advanced Genetics of Human Diseases	Completed
iii. Statistical Methods in Genetic Epidemiology	Completed
iv. Teaching and Mentoring	Completed
b. Prepare additional grants to support dissertation research	Completed
c. Conduct data analysis on existing breast cancer data	Completed[2]
d. Serve as Lead teaching assistant for Introduction to Epidemiology	Completed
e. Conduct research on active learning techniques in Introduction to Epidemiology	Completed[3]

Task 3: Project Oversight of Genotyping of Samples (Months 5-24)	
a. Monitor progress of assay development and implementation	Completed
b. Perform data management and project oversight	Completed
c. Perform independent quality assurance of 10% of samples at FHCRC (n = 237)	Completed; modified task[4]
d. Apply for and obtain IRB renewal	Completed
Task 4: Training-related Work (Months 13-36)	
a. Present research findings on active learning at the UW Scholarship of Teaching and Learning Symposium	Completed[3]
b. Conduct data analysis on existing data related to breast cancer etiology	Completed[5]
c. Serve as a teaching assistant for Introduction to Genetics	Completed
Task 5: Data Analysis and Report Writing (Months 25-36)	
a. Perform data cleaning and coding of variables	Completed
b. Perform statistical analysis for each Specific Aim	Completed
i. Impute haplotypes using PHASE v.2 software	Completed
ii. Using STATA v.8, perform logistic regression analysis	Completed
iii. Using STATA v.8, perform polytomous regression analysis	Completed
c. Prepare manuscripts	Completed
d. Present results at DOD Era of Hope conference	Completed

[1] Substituted auditing the Biostatistics course, Statistical Evaluation of Biomarkers.
[2] See Appendix 2 for the publication resulting from this work.
[3] Refer to the list of meeting abstracts for presentations of this work.
[4] Modification involved performing a pilot investigation of rare SNPs in the first 2 exons of the PGR gene because quality controls were performed by the laboratory.
[5] Refer to the list of meeting abstracts for presentations of this work.

Appendix 2: Curriculum Vitae.

KERRYN W. REDING, PhD, MPH

Personal Information

Office Address: Fred Hutchinson Cancer Research Center
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Seattle, WA 98109
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Home Address: 4338 2nd Avenue NE
Seattle, WA 98105

Education

Doctor of Philosophy, 2008
Department of Epidemiology
University of Washington, Seattle
Dissertation: *Investigation of Genetic Polymorphisms in the Progesterone and Estrogen Pathways as Modifiers of the Effect of Hormone Therapy on Breast Cancer*

Master of Public Health, 2002
Department of Epidemiology
Genetics Interdepartmental Concentration
University of Michigan, Ann Arbor
Thesis: *Racial Disparities in Endometrial Cancer: An Investigation of Smoking as a Socially Patterned Exposure Affecting the Rates of Mutation in TP53 Among Black and White Women*

Bachelor of Science, May 1998
Major: Zoology
Arizona State University Honors College, Tempe
Honors Thesis: *Consequences of Genetic Testing for Female Breast Cancer*

Awards

Post-doctoral Fellow, Cancer Epidemiology and Biostatistics Training Grant, National Institutes of Health (NIH), 2008

Scholar in Training Award, Molecular Epidemiology Working Group, American Association of Cancer Research (AACR), Annual Meeting, 2007

Scholar in Training Award, AACR, New Developments in the Epidemiology of Cancer Prognosis, 2006

Pre-doctoral Fellow, Cancer Epidemiology and Biostatistics Training Grant, NIH, 2003-2006

Founders Fellowship, Achievement Reward for College Scientists (ARCS), University of Washington, 2003-2006

Dean's Award, Full Tuition Scholarship, University of Michigan, 2000-2002

Summa cum Laude Graduate, Arizona State University, 1998

National Kappa Alpha Theta Scholarship, 1997

Regent's Full Tuition Scholarship, Arizona State University, 1994-1998

Funded Grants

Department of Defense (DOD) Breast Cancer Research Program Pre-doctoral Training Grant, 2006. PI: **Kerryn W. Reding**; $90,000 (direct costs).

Center for Ecogenetics and Environmental Health, University of Washington, pilot project "Genetic polymorphisms as modifiers of the effect of HRT on the risk of breast cancer", 2005. PI: Kathleen E. Malone; $25,000 (direct costs); co-author.

National Cancer Institute, R03 "Breast Cancer and HRT: genetic susceptibility within the progesterone pathway," 2005; PI: Kathleen E. Malone; $100,000 (direct costs); co-author.

Academic Appointments

RESEARCH

Post-doctoral Fellow, 2008- current
Fred Hutchinson Cancer Research Center
Epidemiology, Public Health Sciences

- Conduct data analyses and prepare manuscripts relating to investigation of factors associated with breast cancer incidence, recurrence, and mortality
    - Genetic polymorphisms in hormonal pathways and the risk of breast cancer
    - Environmental factors interacting with BRCA1 and BRCA2 mutations in breast cancer recurrence
    - Effect of exercise on prolactin levels within women in the APPEAL randomized trial
    - Effect of weight change after diagnosis on mortality among breast cancer patients

Research Assistant, 2004-2008
Fred Hutchinson Cancer Research Center
Cancer Epidemiology Research Cooperative, Public Health Sciences
Primary Mentor: Kathleen Malone

- Took primary role in writing 3 grants submitted to the National Cancer Institute, Department of Defense, and Center for Ecogenetics and Environmental Health
- Performed study management duties and oversight of laboratory work
- Conducted data analyses and drafted manuscripts

Research Assistant, 2001 - 2003
University of Michigan, Department of Epidemiology
Genes, Environment, and Melanoma Study
Primary Mentor: Stephen B. Gruber

- Performed DNA sequencing on tumor samples and data analysis
- Recruited and interviewed study subjects

TEACHING

Adjunct Instructor, Fall Quarter 2005, 2006
Bastyr University
Introduction to Biostatistics: TR 5100

- Taught required course for students in the Masters program in Nutrition and Exercise Science
- Prepared course materials, lectures, and exams
- Supervised a teaching assistant

Teaching Assistant, Spring Quarter 2005, 2006
University of Washington
Undergraduate Introduction to Epidemiology: EPI 420
Professor: Jack Goldberg

- Led weekly discussion sections in which I employed active learning strategies
- Served as lead Teaching Assistant, 2006

Huckabay Teaching Fellowship, 2004-2005
University of Washington

- Designed and implemented problem-based learning modules for undergraduate Introductory Epidemiology courses at Seattle University and University of Washington

Teaching Assistant, Fall Quarter 2004 and Winter Quarter 2005
University of Washington
Epidemiologic Methods: EPI 512, EPI 513
Professors: Thomas D. Koepsell and Noel S. Weiss

- Led in-class discussions, held office hours, graded weekly homework and exams for this graduate-level course which serves as a cornerstone in the Epidemiology curriculum

Other Work Experience

Computer Software Developer, 1998 - 2000
Andersen Consulting

- Designed, developed, and tested software for financial services industry
- Supervised and mentored a student intern to develop marketable software skills

Manuscripts

Kerryn W. Reding, Janet R. Daling, Cecilia A. O'Brien, David R. Doody, Peggy L. Porter, and Kathleen E. Malone. "The Effect of Pre-Diagnostic Alcohol Consumption on Survival after Breast Cancer in Young Women." Cancer Epidemiol Biomarkers Prev 2008; 17 1988-1996.

Kerryn W. Reding, Noel S. Weiss, Chu Chen, Christopher I. Li, Christopher S. Carlson, Jasmine Wilkerson, Frederico M. Farin, Kenneth E. Thummel, Janet R. Daling, and Kathleen E. Malone. "Genetic polymorphisms in the catechol estrogen metabolism pathway and breast cancer risk." (Submitted for publication to Cancer Epidemiology Biomarkers and Prevention).

Kerryn W. Reding, Kathleen E. Malone, Bryan Langholz, Colin B. Begg, Leslie Bernstein, Robert W. Haile, Marinela Capinau, Anne Reiner, Xiaolin Liang, Charles F. Lynch, Patrick Concannon, Sharon Teraoka, Lisbeth Bertelsen, Ake Borg, The WECARE Collaborative Study

Group, and Jonine Bernstein. "Adjuvant systemic therapy for breast cancer and the risk of contralateral breast cancer in *BRCA1* and *BRCA2* mutation carriers." (Submitted for publication to Journal of Clinical Oncology).

Book Chapters

Kathleen E. Malone and **Kerryn W. Reding**. "Family History and Breast Cancer Genetics," In: Li, Christopher I, ed., *Breast Cancer Epidemiology*. Springer. (Solicited contribution)

Presentations

INVITED ORAL PRESENTATIONS

Era of Hope Conference, Department of Defense Breast Cancer Research Program, Baltimore, MD, June 2008. "Genetic polymorphisms in the catechol estrogen metabolism pathway as modifiers of the effect of hormone therapy in breast cancer risk." **Kerryn W. Reding**, Chu Chen, Christopher I. Li, Christopher S. Carlson, Jasmine Wilkerson, Frederico M. Farin, Kenneth E. Thummel, Janet R. Daling, and Kathleen E. Malone.

Center for Ecogenetics and Environmental Health Annual Retreat, University of Washington, Seattle, WA, November 2007. "Genetic polymorphisms in the catechol estrogen metabolism pathway as modifiers of the effect of hormone therapy in breast cancer risk." **Kerryn W. Reding**, Chu Chen, Christopher I. Li, Christopher S. Carlson, Jasmine Wilkerson, Frederico M. Farin, Kenneth E. Thummel, Janet R. Daling, and Kathleen E. Malone.

Achievement Reward for College Scientists (ARCS) Members' Meeting, Seattle, WA, May 2005, Presenter. "What We Know About the Genetics of Breast Cancer."

POSTER PRESENTATIONS

4th Annual University of Washington Teaching and Learning Symposium, Seattle, WA, May 2008. "Innovative Teaching Methods for a Large Introductory Epidemiology Course." Yuzo Arima, **Kerryn W. Reding**, Britton Trabert, Zoe Edelstein, Sara Nelson, Kathryn Adeney, Amy Poel, and Jack Goldberg.

American Association of Cancer Researchers (AACR) Annual Meeting, Los Angeles, CA, April 2007, "Genetic polymorphisms in the estrogen metabolism pathway as modifiers of the effect of hormone therapy in breast cancer risk." **Kerryn W. Reding**, Chu Chen, Christopher I. Li, Christopher S. Carlson, Jasmine Wilkerson, Frederico M. Farin, Kenneth E. Thummel, Janet R. Daling, and Kathleen E. Malone.

2nd Annual University of Washington Teaching and Learning Symposium, Seattle, WA, April 2006. "Using Formative Assessments as a Student-Centered Approach to Improving the Implementation of Problem-Based Learning Modules." **Kerryn W. Reding**, Deborah Hatch, Lawrence Wechsler, and Thomas D. Koepsell.

AACR New Developments in the Epidemiology of Cancer Prognosis Conference, Charleston, SC, January 2006. "The Effect of Pre-Diagnostic Alcohol Consumption on Survival after Breast Cancer in Young Women." **Kerryn W. Reding**, Kathleen E. Malone, Janet R. Daling, Cecilia A. O'Brien, David R. Doody, Peggy L. Porter.

International Society of Scholarship of Teaching and Learning (ISSOTL) Conference, Vancouver, Canada, October 2005. "Using Formative Assessments as a Student-Centered Approach to Improving the Implementation of Problem-Based Learning Modules." **Kerryn W. Reding**, Deborah Hatch, Lawrence Wechsler, and Thomas Koepsell.

AACR Pathobiology Workshop, Snowmass, CO, July 2005. "A Hypothesis of Smoking as a TP53 Mutagen in a Subset of Endometrial Cancers." **Kerryn W. Reding**, Terri Madison, David Schottenfeld, Kathleen R. Cho, Ann Schwartz, Stephen B. Gruber.

Service

Huckabay Teaching Fellowship Information Session, University of Washington Preparing Future Faculty Initiative, Panel Member, 2005, 2006, and 2008.

Student Representative, University of Washington, Epidemiology Department Chair Review Committee, 2007

Student Representative, University of Washington, School of Public Heath and Community Medicine Curriculum Committee, 2006-07

Student Representative, University of Washington Childcare Task Force, 2006

Student Representative, Department of Epidemiology, 2005-2006

Member, American Association of Cancer Research, 2005-current

Mentored undergraduate students from Seattle University on Senior Synthesis Projects, 2004-2005

Mentor, Women In Science and Engineering, 1998-2000

Member, Andersen Consulting Community Outreach Team, 1998-2000

References

(Available upon request)

Scott Davis, PhD
Chair, Department of Epidemiology
University of Washington
sdavis@fhcrc.org

Stephen B. Gruber, MD, PhD
Associate Professor, Epidemiology
University of Michigan
sgruber@u.mich.edu

Mark Kestin, PhD

Dean of Nutrition and Exercise Science Department
Bastyr University
mkestin@bastyr.edu

Kathleen E. Malone, PhD
Full Member, Epidemiology
Fred Hutchinson Cancer Research Center
kmalone@fhcrc.org

Noel S. Weiss, MD, DrPH
Professor, Epidemiology
University of Washington
nweiss@u.washington.edu

Appendix 3: Published Manuscript.

Effect of Prediagnostic Alcohol Consumption on Survival after Breast Cancer in Young Women

Kerryn W. Reding,[1,2] Janet R. Daling,[1] David R. Doody,[1] Cecilia A. O'Brien,[1] Peggy L. Porter,[1] and Kathleen E. Malone[1,2]

[1]Fred Hutchinson Cancer Research Center and [2]University of Washington, Seattle, Washington

Abstract

Background: Alcohol consumption has been comprehensively investigated as an etiologic risk factor for breast cancer but has received little attention in terms of its effect on prognosis after breast cancer, particularly for young women.

Methods: 1,286 women diagnosed with invasive breast cancer at age ≤45 years from two population-based case-control studies in the Seattle-Puget Sound region were followed from their diagnosis of breast cancer (between January 1983 and December 1992) for survival through June 2002, during which time 364 women had died. Cox proportional hazards modeling was used to assess the effect of prediagnostic alcohol consumption on the risk of dying.

Results: After adjusting for age and diagnosis year, compared with nondrinkers, women who consumed alcohol in the 5 years before diagnosis had a decreased risk of death [>0 to <3 drinks per week: hazard ratio, 0.7; 95% confidence interval (95% CI), 0.6-0.95; 3 to <7 drinks per week: risk ratio, 0.6; 95% CI, 0.4-0.8;7 drinks per week: risk ratio, 0.7; 95% CI, 0.5-0.9]. This association was unchanged on additional adjustment for potential confounders including most notably treatment, stage at diagnosis, and mammogram history.

Conclusion: These results suggest that women who consume alcohol before a diagnosis of breast cancer have improved survival, which does not appear to be attributable to differences in stage, screening, or treatment. (Cancer Epidemiol Biomarkers Prev 2008;17(8):1988–96)

Introduction

Although alcohol consumption has been identified as one of the few, known modifiable risk factors for breast cancer (1-5), its possible role in breast cancer recurrence and mortality has received little research attention, particularly in younger women. Light to moderate amounts of alcohol consumption have been associated with lower overall and coronary heart disease–associated mortality among women (6, 7). However, evidence has been sparse and inconsistent for the effect of alcohol consumption on breast cancer mortality in young women (8-10).

There is an indication that the effects of alcohol may take place during late breast carcinogenesis due to the association between alcohol consumption and late-stage breast cancer and lack of association between alcohol and benign proliferative epithelial disorders of the breast (11, 12). Prior etiologic studies have shown that the most relevant timing of exposure for certain exogenous risk factors for breast cancer, including alcohol, may be the years immediately preceding diagnosis (13-15). Furthermore, in a meta-analysis of 38 studies investigating alcohol consumption and breast cancer risk, Longnecker describes the finding that cohort studies with longer follow-up time showed weaker effects of alcohol use on breast cancer incidence, indicating that the salient period for alcohol use was recent use (3).

Given the consistent nature of the association of alcohol and breast cancer risk as well as the common nature of alcohol consumption, we evaluated the effect of prediagnostic alcohol consumption on the risk of death (overall and breast cancer mortality) in a population-based cohort study of breast cancer patients diagnosed at age <45 years, focusing primarily on recent use of alcohol.

Materials and Methods

Study Population. The 1,286 women with invasive breast cancer in the current study were drawn from two previously completed population-based case-control studies of breast carcinoma conducted at the Fred Hutchinson Cancer Research Center. The methods for both studies were essentially the same and have been described previously (16, 17). The cases were identified from the Cancer Surveillance System (CSS), which is part of the Surveillance, Epidemiology, and End Results (SEER) Program, with eligibility criteria for the first study including first primary breast carcinoma diagnosis between January 1983 and April 30, 1990; diagnosed at age <45 years; women born after 1944; and women of Caucasian race. Interviews were completed on 845 women (83.3% of eligible cases). In the second study, cases were also identified through CSS with eligibility criteria including first primary breast carcinoma identified from May 1, 1990 to December 31, 1992;

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Grant support: R01 CA59936; Cancer Epidemiology Training Grant 2 T32 CA 09168 and Department of Defense Breast Cancer Research Program Predoctoral Training Grant 06-1-0312 (K.W. Reding). The original registry-based ascertainment of cases by the CSS, a participant in the SEER Program and was supported by N01-PC35142.

Requests for reprints: Kathleen E. Malone, Fred Hutchinson Cancer Research Center, M4-C308, Box 19024, Seattle, WA 98109-1024. Phone: 206-667-4630; Fax: 206-667-5948. E-mail: kmalone@fhcrc.org

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diagnosed at age <45 years; and women of any race; 643 women (83.9% of eligible cases) were interviewed as part of this study.

In-person interviews conducted through these previous studies included questions ascertaining lifetime history of a variety of known and suspected breast cancer risk factors including prediagnostic history of alcohol consumption and smoking, body size history, and reproductive risk factors. With regard to alcohol use, participants were asked about their volume (number of drinks), frequency (times per day/week/month), and type (beer/wine/liquor) of alcohol use from the time alcohol use began until their diagnosis of breast cancer. Participants self-defined the relevant time spans for the various patterns of consumption of each type of beverage throughout their lives. The protocol of this study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center.

Follow-up. The methods used to follow up the breast carcinoma cases have been reported previously and are summarized only briefly here (18). Active (hospital and physician annual follow-up) and passive (National Death Index) surveillance of vital status of study participants was done by CSS. For women whose cause of death was unavailable through the CSS, death certificates were obtained and causes of death were classified as breast cancer related or not using the CSS protocol. Participants underwent follow-up until the earliest of the date of death, the date last known to be alive, or the end date of our follow-up period (June 2002). Among those not reported to be dead, 93.1% had been contacted within 12 months of the end of the follow-up period.

The primary mortality endpoint used was all-cause mortality. In this age group, deaths from other causes are fairly minimal and the vast majority of deaths were related to breast cancer. Of 364 deaths, 335 (92.0%) were known to be due to breast carcinoma, 22 (6.0%) were due to other causes, and 7 (1.9%) were unknown as to the cause of death. Analyses were repeated using breast cancer death as the mortality endpoint and censoring women with other causes of death at the time of their death and results were unchanged (see Results).

Pathology Review, Testing of Tumor Samples for Prognostic Markers, and Collection of Treatment Information. Tumor specimens were available for a centralized pathology review on 1,019 (79.2%) of the 1,286 breast cancer cases. For the remaining samples, either permission was not given to access the tumor tissues or tumor blocks were not available or had been discarded by the laboratories; 907 (70.5%) cases had adequate tissue samples available for immunoperoxidase assays. Tumors were evaluated for expression of estrogen receptor (ER), progesterone receptor (PR), p53 tumor suppression gene protein, Ki-67 proliferation-related antigen, c-erbB-2 oncogene protein, apoptosis regulatory protein bcl-2, cyclin E protein, S-phase fraction, and p27 protein as described previously (19, 20). Tumors were classified as positive/high staining or negative/low staining based on the percentage of tumor cells staining positive and/or the pathologist's interpretation of staining intensity. For ER, PR, and p53, any nuclear staining was considered positive; the percentage of Ki-67 was averaged over four high-power fields with ≥25% considered high proliferation; for tumor necrosis factor, categories of none and intermediate were combined versus high; for bcl-2, negative and low-intensity stains were categorized as low, whereas intermediate and high-intensity stains were categorized as high.

Women whose tumors were available for analysis were on the whole similar to the women without tumor data available, with the exception that women with available tumor samples were older at diagnosis (80.1% were ages ≥35 years) than the women without tumor samples (72.3%; $P = 0.006$). There were no apparent differences in alcohol consumption or mortality between women whose tumor samples were and were not available for analyses ($P = 0.20$ and 0.32, respectively).

Medical records were abstracted to identify courses of treatment including surgery, radiation therapy, chemotherapy, and/or hormonal therapy; 1,113 cases (86.5%) included in this analysis had their medical record reviewed by trained medical record abstractors. For those participants who refused medical record review, whose records were destroyed, or who had incomplete information with respect to treatment, treatment information was obtained from the follow-up study questionnaires and the CSS.

Statistical Analysis. For the primary analysis focused on recent alcohol consumption, the average weekly alcohol consumption was computed for the period spanning 7 to 2 years before diagnosis. To compute the weekly average number of drinks consumed over this period, we calculated the total number of drinks consumed during the period (summing over all applicable episodes reported) and divided by 260, the total number of weeks in the 5-year period.

Average weekly alcohol consumption was categorized as never or none during this period, >0 to <3, 3 to <7, and ≥7 drinks per week; from this point forward, we refer to these categories as nondrinkers, light, moderate, and heavy drinkers, respectively. A woman who had consumed <12 alcoholic beverages in her lifetime or <1 drink per month for ≥6 months was considered a never drinker. Alcohol consumption during the 2-year period immediately preceding diagnosis was omitted from computations to exclude any disease-related changes in alcohol consumption (15). For the sake of brevity, we will henceforth refer to the 7 to 2 years before diagnosis as the 5 years before diagnosis.

The lifetime average weekly intake of alcohol was determined by calculating the average amount of alcohol consumed per week from age 15 years until diagnosis. We also investigated alcohol exposure by beverage type: wine, liquor, and beer. One drink was defined as 12 ounce beer, 1.5 ounce liquor, and 4 ounce wine.

Estimates of the relative risk of dying were calculated using Cox proportional hazards models. The hazard ratios (HR) were left-truncated to account for the time lag between diagnosis and interview. Censoring occurred at either the date of last known follow-up or the end date of follow-up (June 2002) if death had not occurred before this. Interaction terms were investigated using the likelihood ratio test.

Table 1. Relationship of demographic and tumor characteristics to the risk of dying among women diagnosed with breast cancer at age <45 y from 1983 to 1992

	Alive	Dead	HR* (95% CI)
Age at diagnosis (y)			
<35	179 (65.1)	96 (34.9)	1.0
≥35	743 (73.5)	268 (26.5)	0.9 (0.7-1.1)
Diagnosis year			
Before 1989	358 (65.3)	190 (34.7)	1.0 (Reference)
On or after 1989	564 (76.4)	174 (23.6)	0.8† (0.6-1.0‡)
Ever use of mammogram§			
No	506 (67.1)	248 (32.9)	1.0 (Reference)
Yes	416 (78.2)	116 (21.8)	0.7* (0.6-0.9)
Chemotherapy‖			
No	299 (75.3)	98 (24.7)	1.0 (Reference)
Yes	617 (70.0)	264 (30.0)	0.9 (0.7-1.1)
Radiotherapy‖			
No	414 (70.2)	176 (29.8)	1.0 (Reference)
Yes	502 (73.0)	186 (27.0)	0.9 (0.7-1.1)
Hormone therapy			
No	551 (71.0)	225 (29.0)	1.0 (Reference)
Yes	300 (70.9)	123 (29.1)	1.0 (0.9-1.0)
Stage			
Local	608 (82.5)	129 (17.5)	1.0 (Reference)
Regional	304 (59.6)	206 (40.4)	2.6* (2.1-3.2)
Distant	1 (4.0)	24 (96.0)	22.0* (14.0-34.4)
Tumor size (cm)			
≤2	527 (80.6)	127 (19.4)	1.0 (Reference)
>2-5	326 (65.3)	173 (34.7)	1.9* (1.5-2.4)
>5	51 (50.0)	51 (50.0)	3.0* (2.2-4.2)
Nodal status			
Negative	615 (82.3)	132 (17.7)	1.0 (Reference)
Positive	302 (56.0)	219 (42.0)	1.5* (1.4-1.6)
Body mass index			
Q1	241 (75.6)	78 (24.4)	1.0 (Reference)
Q2	230 (72.8)	86 (27.2)	1.1 (0.8-1.6)
Q3	238 (74.3)	82 (25.6)	1.2 (0.9-1.6)
Q4	205 (63.9)	116 (36.1)	1.9* (1.4-2.5)
Recency of pregnancy (y)			
Nulliparous	251 (74.9)	84 (25.1)	1.0 (Reference)
≥5	529 (74.0)	186 (26.0)	1.1 (0.8-1.4)
2 to <5	97 (67.8)	46 (32.2)	1.3 (0.9-1.9)
<2	45 (48.9)	47 (51.1)	2.2* (1.5-3.0)
First- or second-degree relative with breast cancer			
No	359 (69.2)	160 (30.8)	1.0 (Reference)
Yes	401 (75.8)	128 (24.2)	0.8* (0.6-1.0†)
Smoking			
Never	464 (71.1)	189 (28.9)	1.0 (Reference)
Former	205 (73.5)	74 (26.5)	0.9 (0.7-1.2)
Current	253 (71.5)	101 (28.5)	1.0 (0.8-1.2)
Race			
White	874 (71.8)	344 (28.2)	1.0 (Reference)
Black	12 (54.6)	10 (45.4)	2.4* (1.2-4.5)
Asian/Pacific Islander	31 (77.5)	9 (22.5)	1.0 (0.5-2.0)
Income ($)			
<15,000	85 (65.9)	44 (34.1)	1.0 (Reference)
15,000-50,000	483 (69.1)	216 (30.9)	0.9 (0.7-1.3)
≥50,000	349 (77.7)	100 (22.3)	0.7* (0.5-1.0†)
Education			
Less than high school	30 (71.4)	12 (28.6)	1.0 (Reference)
High school/some college	560 (71.0)	229 (29.0)	1.2 (0.7-2.2)
College graduate	332 (73.0)	123 (27.0)	1.2 (0.6-2.1)

*Adjusted for age, mammogram, and diagnosis year, except as noted.
†Statistically significant HR.
‡1.0 due to rounding; 95% CI excludes 1.0.
§Adjusted for age and diagnosis year.
‖Adjusted for age, diagnosis year, nodal status, stage, and tumor size.

Age and reference year were accounted for in all analyses. We assessed the following factors for their potential confounding or modifying effects: mammogram history (defined as ever having a mammogram), smoking history (never, former, current), body mass index (quartiles), education (less than high school, high school/some college, graduated college), income (<$15,000/yr, $15,000-50,000/yr, >$50,000/yr), race (Caucasian, African American, Asian, other), and oral contraceptive use (never, <10 years, ≥10 years).

The Mantel-Haenszel χ^2 test was used for all bivariate analyses. To be included as a potential confounder in the multivariate analysis, we required that a variable be associated with both alcohol consumption and the outcome. Variables that altered the estimate in the multivariate model by ≥10% were retained in the final model. The variables meeting these criteria within the Cox proportional hazards model were age and year of diagnosis and mammogram history.

We examined the association between alcohol consumption and tumor characteristics using logistic regression to assess the odds of breast cancer with specific tumor characteristics and reported odds ratios (OR) and 95% confidence interval (95% CI). An investigation into the potential confounding factors involved in this analysis indicated that age at diagnosis, diagnosis year, and smoking history all met the criteria, as set forth above, for confounding and thus were included in the logistic regression model.

Results

The association between mortality and demographic features and tumor characteristics is shown in Table 1. Women diagnosed before 1989 had a greater risk of dying; women reporting a history of a prior screening mammogram had a reduced risk of dying. As would be expected, tumor characteristics known to be unfavorable, including larger tumor size, later stage at diagnosis, and positive nodal status, were all associated with an increased risk of mortality in this cohort. As shown previously in this data set, the highest quartile of body mass index (≥25.8 kg/m^2) was associated with an increased risk of mortality compared with the first quartile (≤20.6 kg/m^2); the recency of pregnancy increased the risk of mortality compared with nulliparous women; women with a first- or second-degree relative with breast cancer were at a lower risk of mortality compared with women with no family history

Table 2. Relationship between alcohol consumption and factors observed to influence the risk of dying among women diagnosed with breast cancer at age <45 y from 1983 to 1992

	Alcohol consumption status in the 5 years before diagnosis		
	Nondrinkers*	Drinkers	*P*
Age at diagnosis (y)			
<35	50 (18.2)	224 (81.8)	0.002
≥35	274 (27.1)	736 (72.9)	
Ever had a mammogram			
No	175 (23.2)	579 (76.8)	0.046
Yes	149 (28.1)	381 (71.9)	
Oral contraceptive use (y)			
Never	99 (34.1)	191 (65.9)	<0.0001
<10	199 (24.3)	621 (75.7)	
≥10	26 (14.9)	148 (85.1)	
Diagnosis year			
Before 1989	93 (17.0)	454 (83.0)	<0.0001
On or after 1989	231 (31.3)	506 (68.7)	
Race			
White	287 (23.6)	929 (76.4)	<0.0001
Black	12 (54.6)	10 (45.4)	
Asian/Pacific Islander	23 (57.5)	17 (42.5)	
Education			
Less than high school	12 (28.6)	30 (71.4)	0.29
High school/some college	205 (26.0)	583 (74.0)	
College graduate	107 (23.6)	347 (76.4)	
Income ($)			
<15,000	31 (24.0)	98 (76.0)	0.17
15,000-50,000	191 (27.4)	506 (72.6)	
≥50,000	98 (21.8)	351 (78.2)	
Recency of pregnancy (y)			
Nulliparous	65 (19.4)	270 (80.6)	0.84
≥5	209 (29.3)	505 (70.7)	
2 to <5	33 (23.1)	110 (76.9)	
<2	16 (17.6)	75 (82.4)	
Smoking			
Never	212 (32.6)	439 (67.4)	<0.0001
Former	52 (18.6)	227 (81.4)	
Current	60 (16.9)	294 (83.1)	
Body mass index			
Q1	70 (22.0)	248 (78.0)	0.0002
Q2	59 (18.7)	256 (81.3)	
Q3	83 (25.9)	237 (74.1)	
Q4	106 (33.0)	215 (67.0)	

*Nondrinkers include those who did not drink during the 5-y period as well as those who did not drink in their lifetime.

Table 3. Risk of dying after breast cancer in relation to level of alcohol consumption among women diagnosed with breast cancer at age <45 y from 1983 to 1992

Average weekly alcohol consumption as drinks per week	Alive	Dead	HR* (95% CI)
5 y before diagnosis			
Nondrinkers†	216 (67.1)	106 (32.7)	1.0 (Reference)
Drinkers	701 (73.4)	254 (26.6)	0.7‡ (0.5-0.9)
>0 to <3	370 (72.0)	144 (28.0)	0.7‡ (0.6-1.0)§
3 to <7	150 (78.1)	42 (21.9)	0.6‡ (0.4-0.8)
≥7	181 (72.7)	68 (27.3)	0.7‡ (0.5-0.9)
Wine drinkers			
Non-wine drinkers	307 (67.6)	147 (32.4)	1.0 (Reference)
Wine drinkers	615 (73.9)	217 (26.1)	0.7‡ (0.6-0.9)
>0 to <3	430 (72.9)	160 (27.1)	0.8 (0.6-1.1)
3 to <7	100 (75.8)	32 (24.2)	0.7 (0.5-1.1)
≥7	85 (77.3)	25 (22.7)	0.7 (0.5-1.1)
Beer drinkers			
Non-beer drinkers	503 (70.8)	207 (29.2)	1.0 (Reference)
Beer drinkers	412 (72.5)	156 (27.5)	0.9 (0.7-1.1)
>0 to <3	309 (72.7)	116 (27.3)	0.9 (0.7-1.1)
3 to <7	55 (75.3)	18 (24.7)	0.8 (0.5-1.2)
≥7	48 (68.8)	22 (31.4)	1.0 (0.6-1.5)
Liquor drinkers			
Non-liquor drinkers	353 (70.9)	145 (29.1)	1.0 (Reference)
Liquor drinkers	567 (72.1)	219 (27.9)	0.9 (0.7-1.1)
>0 to <3	460 (72.3)	176 (27.7)	0.9 (0.7-1.1)
3 to <7	53 (68.0)	25 (32.0)	1.1 (0.6-1.5)
≥7	54 (75.0)	18 (25.0)	0.8 (0.5-1.2)
Over the lifetime			
Never drinkers	160 (65.8)	83 (34.2)	1.0 (Reference)
Ever drinkers	756 (73.0)	280 (27.0)	0.7‡ (0.5-0.8)
>0 to <3	432 (74.0)	152 (26.0)	0.6‡ (0.5-0.8)
3 to <7	178 (70.6)	74 (29.4)	0.7‡ (0.5-1.0)§
≥7	146 (73.0)	54 (27.0)	0.6‡ (0.5-0.9)

*Adjusted for age, diagnosis year, and mammography.
†Nondrinkers include those who did not drink during the 5-y period as well as those who did not drink in their lifetime.
‡Statistically significant HR.
§Due to rounding, $P < 0.05$.

(18, 19, 21). Higher income (≥$50,000/yr) was associated with reduced mortality compared with income of <$15,000/yr. However, education was not associated with mortality. Compared with White women, Black women were found to be at increased risk of mortality, whereas Asian women were not.

Factors associated with mortality after breast cancer were examined for their relationship with alcohol consumption in the 5-year period before diagnosis (Table 2). Most of these factors varied significantly by alcohol consumption status, including age at diagnosis, mammogram history, history of oral contraceptive use, diagnosis year, race, smoking status, and quartile of body mass index.

Compared with women who reported no alcohol consumption in the 5-year period before diagnosis, women who consumed alcohol during the same interval had a 30% reduction in the risk of dying after breast cancer (0.7; 95% CI, 0.5-0.9; Table 3). This reduction in the risk of dying did not vary substantively based on the average number of drinks consumed [compared with nondrinkers, the risk of death was 0.7 (95% CI, 0.6-0.95) for light drinkers, 0.6 (95% CI, 0.4-0.8) for moderate drinkers, and 0.7 (95% CI, 0.5-0.9) for heavy drinkers]. We found similar patterns of risk in relation to average lifetime alcohol consumption.

These and all other HR reported henceforth were adjusted for age, diagnosis year, and mammography. The association between recent alcohol consumption and the risk of dying was not altered by adjustment for any additional potential confounders. Further, adjustment for factors related to mortality (stage, histologic grade, and treatment factors) did not change results [compared with nondrinkers: HR, 0.7 (95% CI, 0.5-0.9) for light drinkers; HR, 0.5 (95% CI, 0.3-0.7) for moderate drinkers; and HR, 0.6 (95% CI, 0.4-0.8) for heavy drinkers]. In addition, there was no evidence of significant effect modification by body mass index, smoking, or age.

Further examination by beverage type revealed that this reduction in risk of dying associated with recent alcohol consumption was limited to wine consumption (risk ratio, 0.7; 95% CI, 0.6-0.9). These results were unchanged when adjusted for beer and liquor drinking. There was no association observed with beer or liquor consumption (Table 3).

To assess possible mechanisms underlying the association between alcohol and improved survival, we examined the relationship of recent alcohol consumption to selected tumor characteristics that are markers of adverse prognosis. Alcohol consumption was unrelated to ER or PR status, Bcl-2 expression, stage, or percentage of tumor cells in S phase (Table 4). Alcohol consumption was related to reduced odds of having a tumor with high tumor necrosis levels (OR, 0.6; 95% CI, 0.4-0.98) and marginally to p53-positive tumors (OR, 0.7; 95% CI, 0.5-1.0).

Including p53 and tumor necrosis in the Cox model for recent alcohol use did not affect the significance of the association for moderate drinkers (HR, 0.5; 95% CI,

0.3-0.8) or heavy drinkers (HR, 0.7; 95% CI, 0.5-0.98) but did affect the statistical significance for light drinkers (HR, 0.8; 95% CI, 0.6-1.1).

Finally, we examined our main results to assess variation according to several sources of effect modification or bias. Results were similar to those reported above when analyses were restricted to premenopausal women [compared with nondrinkers: HR, 0.7 (95% CI, 0.6-0.96) for light drinkers; HR, 0.5 (95% CI, 0.4-0.8) for moderate drinkers; and HR, 0.7 (95% CI, 0.5-0.95) for heavy drinkers]. Results were also unchanged when we restricted to deaths due to breast cancer [excluding the small number of non-breast cancer-related deaths; HR, 0.7 (95% CI, 0.6-0.97) for light drinkers; HR, 0.6 (95% CI, 0.4-0.9) for moderate drinkers; and HR, 0.7 (95% CI, 0.5-0.9) for heavy drinkers]. Additionally, because this study retrospectively ascertained breast cancer cases in 1983 to 1985, we repeated analyses excluding cases diagnosed before 1986 and again found that our results were unchanged [HR, 0.7 (95% CI, 0.6-0.96) for light drinkers; HR, 0.6 (95% CI, 0.4-0.8) for moderate drinkers; and HR, 0.6 (95% CI, 0.5-0.9) for heavy drinkers]. Also, as this analysis combined two study populations, we conducted the analysis separately within each study and found similar results in each study, although individually these results lack the same precision as found in the combined analysis due to the smaller sample sizes [in the study conducted with women diagnosed from 1983 to 1990: HR, 0.8 (95% CI, 0.6-1.1) for light drinkers; HR, 0.6 (95% CI, 0.4-0.96) for moderate drinkers; and HR, 0.8 (95% CI, 0.5-1.1) for heavy drinkers; in the study conducted with women diagnosed from 1990 to 1992: HR, 0.7 (95% CI, 0.5-1.0) for light drinkers; HR, 0.5 (95% CI, 0.3-0.95) for moderate drinkers; and HR, 0.6 (95% CI, 0.3-1.0) for heavy drinkers]. Lastly, in analyses restricted to women with available tumors, the results were unchanged [HR, 0.7 (95% CI, 0.6-0.97) for light drinkers; HR, 0.5 (95% CI, 0.3-0.7) for moderate drinkers; and HR, 0.6 (95% CI, 0.5-0.9) for heavy drinkers].

Discussion

In the interpretation of the above findings, we should consider the limitations of our study. First, we were unable to interview 15% of the women eligible for the original case-control studies on which this population-based cohort study was based. At 5 years, 43.5% of the noninterviewed cases and 14.5% of the interviewed cases were deceased. To the extent that noninterviewed cases differ from interviewed cases based on their alcohol consumption, our results may be biased. Because this differential was greatest for women in the earliest years of the cohort (due to a lag in interviewing), we assessed its potential effect through a subset analysis limited to women diagnosed after 1986. The absence of any change in results suggests that our results may be generalizable to the entire spectrum of breast cancer cases. A second potential limitation was the possibility of confounding. Despite the breadth of data available to us to assess potential confounding influences, including comprehensive treatment data and other lifestyle variables, we could not exclude the possibility of unmeasured or residual confounding that accounts for our findings.

Additionally, this study did not collect information on dietary factors, and as a result, we were unable to

Table 4. Relationship of average weekly alcohol consumption in 5 y before diagnosis to tumor characteristics

Alcohol consumption*	Tumor characteristic		OR (95% CI)†
ER	Positive	Negative	
Nondrinkers	148 (27.7)	92 (25.1)	1.0 (Reference)
Drinkers	386 (72.3)	274 (74.9)	1.1 (0.8-1.4)
PR	Positive	Negative	
Nondrinkers	150 (27.6)	89 (25.1)	1.0 (Reference)
Drinkers	394 (72.4)	266 (74.9)	1.0 (0.7-1.4)
Tumor necrosis factor	None-intermediate	High	
Nondrinkers	222 (25.5)	35 (33.3)	1.0 (Reference)
Drinkers	650 (74.5)	70 (66.7)	0.6‡ (0.4-1.0)§
Ki-67	Low	High	
Nondrinkers	140 (26.0)	98 (27.8)	1.0 (Reference)
Drinkers	399 (74.0)	255 (72.2)	0.9 (0.7-1.3)
Bcl-2	High	Low	
Nondrinkers	109 (28.9)	128 (24.8)	1.0 (Reference)
Drinkers	266 (70.9)	389 (75.2)	1.3 (0.9-1.7)
p53	Negative	Positive	
Nondrinkers	132 (24.6)	105 (29.3)	1.0 (Reference)
Drinkers	405 (75.4)	254 (70.8)	0.7 (0.5-1.0)
% S phase	Low	High	
Nondrinkers	80 (24.6)	92 (28.1)	1.0 (Reference)
Drinkers	245 (75.4)	235 (71.9)	0.8 (0.5-1.1)
Stage	Local	Regional/distant	
Nondrinkers	183 (24.9)	137 (25.7)	1.0 (Reference)
Drinkers	551 (75.1)	396 (74.3)	1.1 (0.8-1.4)
Grade	Low/intermediate	High	
Nondrinkers	137 (25.3)	116 (26.9)	1.0 (Reference)
Drinkers	405 (74.7)	315 (73.1)	1.2 (0.9-1.6)

*During the 5-y period before diagnosis, nondrinkers include those who did not drink during the 5-y period.
†Adjusted for age, diagnosis year, and smoking status.
‡Statistically significant OR.
§Due to rounding, $P < 0.05$.

examine whether dietary factors may modify the effect of alcohol consumption on risk of death. In addition, because this study was done in a sample of predominantly White women, reflecting to a great extent the underlying racial distribution of the Seattle-Puget Sound area, we cannot be sure these results are generalizable to non-White populations. Lastly, the ascertainment of alcohol exposure relied on self-reported drinking history. The interviewer-guided questionnaires were developed to chart the pattern of exposure beginning with the age at which alcohol consumption began and document the changes in this pattern over time. Overall, the quantity/frequency method for ascertaining alcohol exposure is a reliable approach to estimate alcohol use and the accompanying strategy of using a lifetime calendar with milestones noted further facilitated recall (22). In our analysis, we found an effect achieved by any intake of alcohol and the magnitude of this association did not vary further according to levels of alcohol consumption; thus, misclassification within different categories of use would have minimal effect on the interpretation of our results. Because any misclassification resulting from this is likely to be nondifferential, misclassification in this case would lead to an attenuation of the real effect of alcohol in our results.

The strengths of this study are also worth noting, including the population-based design, which heightens the generalizability of the results, the large sample size, particularly the large numbers of very young cases, and the centralized pathologic review and laboratory analyses done on tissue samples.

Our results indicate that young women who consumed alcohol before a diagnosis of breast carcinoma were at a decreased risk of mortality compared with women who consumed no alcohol. There was some suggestion that the decreased risk of death was limited to wine consumption. This reduction in risk of dying does not appear to be due to differences in mammography screening history, tumor characteristics, treatment, or other exposures.

Little research has been focused on the association between alcohol and risk of dying after a breast cancer diagnosis, particularly among young women. Several studies have found results broadly similar to ours in terms of the direction and magnitude of effects, although in general these studies represent an older demographic than ours. In the Saxe et al. study, although the risk of death among premenopausal breast cancer cases associated with alcohol consumption did not reach statistical significance (HR, 0.41; 95% CI, 0.01-16.35 per 2 drinks per day), the magnitude of the observed effect was consistent with our findings. Their sample of 149 breast cancer patients consisted of 51 (34.2%) premenopausal and 98 (65.8%) postmenopausal women with a median age of 57.8 years (in our study, 92.5% were premenopausal). Similarly, Holmes et al. observed a decreased risk of death among breast cancer cases in relation to prior alcohol consumption in the Nurses' Health Study. However, these results also failed to reach statistical significance [HR (95% CI), 0.79 (0.61-1.02), 0.86 (0.63-1.16), and 0.92 (0.66-1.27) for the second, third, and fourth quartiles, respectively, compared with the first quartile of alcohol consumption; ref. 23]. Although this study had a generous sample size of 1,982 women with invasive breast cancer, it reflected a wider age spectrum and older age group than ours, with a mean age of 54 years (versus our study's 37.7 years). Lastly, Zhang et al. observed a nonstatistically significant reduction in risk of death for women consuming ≥4 g/d alcohol (risk of death, 0.7; 95% CI, 0.3-1.5) in a data set of 698 breast cancer patients ages 55 to 69 years at baseline (24).

Some studies with results that conflict with ours include the study of Hebert et al., who observed in their hospital-based cohort of 546 early-stage breast cancer cases that beer (but not wine or liquor) consumption was related to an increased risk of breast cancer mortality among premenopausal women (8). McDonald et al., in a hospital-based cohort of 125 postmenopausal African American breast cancer cases found prediagnostic consumption of at least 1 drink per week was associated with a 2.7 times greater risk of all-cause mortality (25). The inconsistencies in these epidemiologic studies, as a whole, potentially reflect the heterogeneity of alcohol as an exposure and the relatively small samples of breast cancer patients that have been studied in many of these analyses. Additionally, there is reason to believe that premenopausal and postmenopausal breast cancer development differs (26); thus, potentially the effect of alcohol on tumorigenesis differs among premenopausal and postmenopausal women, which would create inconsistencies across studies with different age ranges.

Previous studies have not investigated the role of prediagnostic alcohol use on tumor characteristics in young women. Our data indicate that the role of alcohol in decreasing the risk of death among breast cancer death may be through its effect on reducing the risk of p53-positive tumors and tumors with high necrosis levels, both of which are associated with decreased survival. However, adjusting for these factors did not fully explain the association of alcohol with improved mortality, particularly in moderate and heavy drinkers.

A potential mechanism involving alcohol consumption in breast cancer survival includes the role of genes involved in metabolism of drugs and other toxins, such as the cytochrome *P*450 and glutathione *S*-transferase enzymes. Some of the women who chose not to drink may have a deficiency in their metabolism of alcohol causing their bodies to react unfavorably to the ingestion of alcohol; this same subset of women could also experience poor metabolism of chemotherapeutic agents based on poor drug metabolism, resulting in higher toxicity to typical doses. This mechanism would require the genes involved in alcohol metabolism to be the same genes involved in chemotherapy metabolism. Some support for the hypothesis that chemotherapy and alcohol metabolism operate in a shared pathway is the observation that alcohol and certain chemotherapeutic agents, including methotrexate and 5-fluorouracil, are involved in the folate pathway (27-29).

Interestingly, several studies have shown an interaction between folate and alcohol in breast cancer, indicating that the effect of alcohol on breast cancer incidence may be reduced by dietary folate (29, 30). The role of folate in breast cancer development is complex with indications that folate has a dual nature in tumorigenesis involving mechanisms that are anticarcinogenic and procarcinogenic depending on the timing and dose of folate (31-33). In breast cancer development, a hypothesis involving folate and alcohol could include the anticarcinogenic (e.g., DNA repair capabilities)

properties of folate being diminished by alcohol consumption, which is compatible with the increased breast cancer risk associated with low folate levels occurring only among regular alcohol drinkers (30). However, with regard to survival from breast cancer, it is less clear how folate and alcohol would interact. Perhaps, alcohol diminishes the amount of folate available; thus, the procarcinogenic properties (e.g., increased proliferation) of folate that are proposed to occur later in tumor development are diminished, which is consistent with the timing of the effects of alcohol as suggested to occur later in tumorigenesis. This would be compatible with the finding in our data that alcohol consumption did not lead to tumors with high proliferation as indicated by the Ki-67 index; however, we were unable to directly test a mechanism involving folate because our study did not collect information on dietary factors.

Current hypotheses regarding the role of alcohol in breast cancer etiology include the effect of alcohol on circulating hormone levels (11). Recent findings from the European Prospective Investigation into Cancer and Nutrition cohort showed that levels of dehydroepiandrosterone, free testosterone, and estrone increase as alcohol consumption increases in premenopausal and postmenopausal women. However, no statistically significant increase was observed for estradiol, free estradiol, or sex hormone binding globulin in response to increasing alcohol consumption in premenopausal women (34). Additionally, alcohol has been shown to increase proliferation in ER-positive, but not ER-negative, breast cancer cell lines (35). Our data did not provide support for the role of alcohol in breast cancer survival to involve hormones in that there were no clear associations with hormone-related tumor markers. This would make sense if alcohol acts later in tumorigenesis when some of the tumor features, such as ER/PR status, have already been established.

Additionally, a hypothesis involving insulin-like growth factor has been developed to explain the increased risk of breast cancer associated with alcohol consumption (36). In response to the observation that breast cancer risk did not increase further within the highest level of alcohol consumption (4, 29), Hu hypothesized that insulin-like growth factor levels decrease as a result of impaired liver function due to high consumption of alcohol (29, 37). With the observation that breast cancer risk was associated with high serum levels of insulin-like growth factor in premenopausal women (38), Jones and Clemmons put forth a mechanism for the role of insulin-like growth factor in carcinogenesis involving the mitogenic effects of insulin-like growth factor and suppression of apoptosis, which counteracts the role of wild-type p53 protein (39). It is possible that plasma insulin-like growth factor levels, as mediated by alcohol, are reduced; thus, the role of the wild-type p53 protein is more pronounced in tumorigenesis among women who consume alcohol; therefore (and as our data suggest), variant p53 would play a greater role proportionately in the tumors of alcohol drinkers.

In addition, with the suggestion in our results that wine, but not beer or liquor, may reduce the risk of death among breast cancer patients, we speculate that components of wine such as polyphenols (e.g., reservatrol and cinnamic acid) could be contributory factors. Several long-term epidemiologic cohort studies have shown that wine is associated with a decreased overall mortality and that the effect is not as strong or not observed at all in drinkers of beer or liquor (40). Research investigating the protective effects of wine has mostly centered around mechanisms involved in cardiovascular disease, including the antioxidant effects of polyphenols (41, 42). In cancer, it is possible that the antioxidant properties of the components of wine have a role in decreasing the process of tumorigenesis, although their role in survival would be less clear. Perhaps in breast cancer, the pathway leading to p53-negative tumors and low necrosis levels in tumors are mediated by the antioxidant effects of polyphenol.

Although alcohol may increase the risk of developing breast cancer in young women (1-3, 5), an age group where tumors tend to be aggressive and mortality is high, it does not appear to have an adverse effect on progression. The results from this study suggest that women who consume alcohol before a diagnosis of breast cancer have improved survival compared with nondrinkers, which does not appear to be attributable to differences in stage, screening, treatment, or other confounders. Our results do not exclude the possibility that abstainers are at an increased risk of death due to the potential clustering of confounders for which we were unable to adjust, and may be separate from the biologic pathways, such as inability to metabolize alcohol adequately, as we discussed above. The findings presented here need to be replicated in similar study populations with an emphasis on elucidating mechanisms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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